

**THE ROLE OF NEURAL PLASTICITY IN THE MECHANISMS AND
TREATMENT OF TINNITUS**

Capstone Project

Presented in Partial Fulfillment of the Requirements for
the Doctor of Audiology
in the Graduate School of The Ohio State University

By

Ashleigh Wells

The Ohio State University
2011

Capstone Committee:

Dr. Gail Whitelaw, Advisor

Dr. Christina Roup

Dr. Lawrence Feth

Approved by

Advisor

ABSTRACT

Tinnitus, or the perception of sound in the absence of an external acoustic stimulus, is a widely investigated yet elusive phenomenon. However, much of the research surrounding tinnitus focuses on the concept of neural plasticity, or the notion that the brain is a dynamic, malleable entity capable of adaptation based on internal and external input. This review will utilize neural plasticity as a framework to explore proposed peripheral and central mechanisms of tinnitus, as well as current trends in tinnitus treatment methodology.

DEDICATION

I would like to dedicate this capstone to my partner, Sean, and my parents, Randy and Peter, for always providing words of encouragement, patience and comedy.

ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Gail Whitelaw, whose enthusiasm and support has allowed me to obtain a deeper understanding and appreciation for such complex subject matter. I also wish to acknowledge my committee, Dr. Christina Roup and Dr. Lawrence Feth, for their counsel and assistance.

VITA

September 29, 1981 Born – Cleveland, Ohio

June 12, 2011..... Doctor of Audiology,
The Ohio State University

2008 – 2010..... Teaching and Research Assistant,
The Ohio State University

2010 – 2011..... Audiology Extern
The Washington DC VA Medical Center

FIELDS OF STUDY

Major Field: Audiology
Specialization: Neuroscience

TABLE OF CONTENTS

	<u>Page</u>
Abstract	ii
Dedication	iii
Acknowledgments	iv
Vita.	v
List of Tables.	vii
List of Figures	viii
Chapters	
1. Neural Plasticity.	1
2. Mechanisms of Tinnitus.	9
3. Tinnitus Treatment.	21
4. The Future of Tinnitus	33

LIST OF TABLES

<u>Table</u>		<u>Page</u>
1	Outcome Measures for Cochlear Implant Candidates	5

LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
1	Block Diagram: Jastreboff's Neurophysiologic Model.	14
2	THI outcome measures for those in TRT treatment group.	25

CHAPTER 1

Neural Plasticity

Ringing, hissing, buzzing, humming, roaring, whistling, clicking; tinnitus is a complex and poorly understood phenomenon categorically defined as the perception of sound in the absence of an external acoustic stimulus (Martines, Bentivegna, Martines, Sciacca, & Martinciglio, 2010). Although an abundance of research has been published in the arena of tinnitus, its definitive etiology and optimal treatment methodology remain disputed and indeterminate. However, the majority of current medical and audiological research revolves around the concept of neural plasticity, or the theory that neural connections within the brain do not maintain a constant state of stasis. Rather, these connections naturally evolve based on external and internal input (Saunders, 2007). This review will utilize a neuroplastic framework to review the myriad mechanisms and treatment methodologies associated with tinnitus.

A recent study by Shargorodsky, Curhan, and Farwell (2010) indicated that an estimated 50 million adults in the United States reported tinnitus, yielding an overall prevalence of 25.3% and a peak prevalence of 14.3% in the 60-69 year old age range. Specifically, the occurrence of tinnitus increases with the age of the patient (Martines et al., 2010). However, of those with tinnitus, approximately 20% exhibit a clinically significant condition, where tinnitus is chronic, intrusive, or debilitating. And, as tinnitus

is typically a subjective experience, clinical significance, or severity, is based on its reported effect on the patient's quality of life (Henry, Dennis & Schechter, 2005; Kennedy, Wilson, & Stephens, 2004).

Chronic tinnitus is often accompanied by hearing impairment, hyperacusis, or reduced sound tolerance, and phonophobia, or a fear of loud sounds, as well as medical conditions including chronic headaches, dizziness, and temporomandibular pain (Kennedy et al., 2004; Tyler, 2000). Furthermore, the psychological effects associated with tinnitus may include irritation, annoyance, anxiety, depression, despair, insomnia, difficulty concentrating, and suicidal ideations, although the psychological profile of the tinnitus patient varies by individual (Centore, 2010; Kennedy et al., 2004; Tyler, 2000). Additionally, the psychological effects of tinnitus can even cause physical responses such as nausea, vomiting, elevation of blood pressure, and increased basal levels of cortisol, a hormone released by the body in response to stress (Hebert & Lupien, 2007; Henry, Dennis & Schechter, 2005; Moller, 2000).

Hebert and Lupien (2007) investigated the cortisol levels of 18 subjects with tinnitus and 18 control participants without tinnitus in response to the Trier Social Stress Test (TSST). The TSST is a standardized protocol meant to induce psychosocial stress in a laboratory setting. The test consists of a 10-minute anticipation period followed by a 10-minute period where research subjects are asked to make a speech and perform oral arithmetic tasks in front of an audience (Kirschbaum, Pirke, & Hellhammer, 1993). Individuals with stress-related disorders often exhibit elevated basal levels of cortisol and blunted cortisol reactivity to stress. The researchers found the 18 subjects with tinnitus displayed a blunted cortisol response to acute stress similar to those with stress-related

disorders like chronic fatigue syndrome and fibromyalgia. The authors suggested this blunted cortisol release response of the tinnitus subjects as empirical and physiological evidence that tinnitus can be categorized as a stress-related disorder (Hebert & Lupien, 2007).

Therefore, tinnitus is a complicated condition with both psychological and physiological effects, and management can be challenging for both the clinician and the tinnitus patient. And, although tinnitus remains an enigmatic phenomenon, investigation into the underlying neurophysiology as well as its possible mechanisms of generation has opened up new avenues for treatment. In turn, hope for improving the quality of life for those with chronic tinnitus is grounded in the research of the past, present and future.

Neural plasticity, or the phenomenon that the brain is a dynamic, malleable entity, has guided research in tinnitus assessment and management. Physiologically, plasticity refers to short- or long-term changes in neuronal sensitivity as a result of modifications to synaptic input (Kaltenbach, Zhang, & Finlayson, 2005; Bartels, Staal, & Albers, 2007). It has been proposed that central reorganization begins at the molecular and cellular level, and can lead to changes in the entirety of areas in the central nervous system. At the psychophysical level, plasticity refers to the induction or alteration of a percept over time (Kaltenbach et al., 2005). In turn, plasticity can be constructive, compensatory and adaptive, or, in the case of tinnitus, may be maladaptive (Saunders, 2007).

Neural plasticity is a familiar concept in the realm of audiology. Current research in hearing aids, cochlear implants, and aural rehabilitation relies on the functional significance of the plastic and adaptive properties of the central nervous system. Specifically, the exploration of plasticity in complementary areas of expertise has served

to lend credence or contradict evidence for the proposed mechanisms and treatment methodologies of tinnitus and its associated conditions.

For example, Munro, Walker, and Purdy (2007) examined evidence for plasticity in elderly hearing aid users fit monaurally with amplification. The authors assessed loudness discomfort levels and acoustic reflex thresholds of 16 elderly patients with symmetrical age-related hearing loss before and after a monaural hearing aid experience. Ipsilateral and contralateral acoustic reflex thresholds and loudness discomfort levels increased significantly in the aided ear when compared to the control ear, showing an asymmetry the authors proposed as evidence of central reorganization as a result of novel auditory input. Moreover, the authors suggested that the neurons affected by the introduction of amplification may have become more successful at coding higher intensity stimuli.

Cervera-Paz, Arbizu, Prieto, and Manrique (2009) explored the potential for central plasticity through positron emission tomography (PET), a measure of cerebral blood flow (rCBF), or metabolic and synaptic activity, using an isotope. The authors hypothesized that PET may be a promising tool in identifying hypometabolism in the primary and associated auditory cortices prior to cochlear implantation. Hypometabolic activity, as opposed to hypermetabolic activity, was suggested as an indicator for increased potential communicatory benefit and improved clinical outcomes. Further, the degree of metabolic activity in the auditory cortex may not only reveal whether a candidate will be successful in speech perception and performance after implantation, but also which ear is optimal for implantation. The authors studied 8 adult cochlear implant candidates where PET was used to select the optimal ear for implantation. Table 1 shows

the type and onset of hearing loss, basal PET results indicating metabolic activity, mode of patient auditory stimulation during PET, and final outcomes for each patient. All implant recipients demonstrated significant improvement in communication performance relative to date of implantation.

Table 1. Sex and age of patients at first visit. In the Ear column, the kind, and type of onset of the hearing loss, and highest performance with hearing aids are shown. Coloured boxes mark the better ear, selected for implantation. Y.O.: year-old; S: severe; P: profound; SNHL: sensorineural hearing loss; HA: hearing aid; SDS: speech discrimination score; HypoM: hypometabolic activity; HyperM: hypermetabolic activity; Sig: significant; N-Sig: non-significant; CI: cochlear implant; NCA: nucleus contour advance; ABH: advance bionic helix; N24: nucleus 24. *Result: at the last follow-up control, indicates highest performance of the implanted ear in closed or open-set monaural condition.

	Right ear	Left ear	PET	Basal	Stimulation	Selection	Result*
Female, 20 years. Student	Congenital idiopathic P-SNHL. No HA	Congenital S-SNHL. Since 4 years. HA 80% SDS	^{18}F -FDG	Right HypoM Left HyperM	Words Bilateral Sig Increase	Right CI Bimodal	Not Implanted
Male, 60 years. Farmer	Meningitic P-SNHL. at 14 years of age. No HA	Meningitic S-SNHL. at 14 years. Since 14 y. HA 75% SDS	^{18}F -FDG	Bilateral normal	Words Bilateral Sig Increase	Right CI (NCA) Bimodal	6 months 32% vowels
Female, 30 years. Physician	Meningitic perilingual P-SNHL. No HA	Meningitic perilingual S-SNHL. Since 4 years. HA 70% SDS	^{18}F -FDG	Bilateral normal	Words Left Sig Increase	Right CI (NCA) Bimodal	6 months 72% vowels 42% consonants
Female, 23 years. Speech therapist (Figure 2)	Ototoxic perilingual P-SNHL. No HA	Ototoxic perilingual S-SNHL. Since 13 HA 50% SDS	^{18}F -FDG	Bilateral HypoM	Words N-Sig Left Increase, Sig Right Increase	Left CI (ABH)	1 year 46% vowels 15% consonants
Female, 64 years. Housewife (Figure 1)	Idiopathic postlingual progressive S-SNHL since 52 years. HA 70% SDS	Idiopathic perilingual P-SNHL. No HA	H_2^{15}O	Left HypoM	Clicks N-Sig Right Increase, Sig Left Increase	Left CI (N24)	2 years 85% disyllables 97% CID sentences
Male, 47 years. Qualified worker	Chronic ear since infancy. P-SNHL at 35 years. HA 60% SDS	Chronic ear and P-SNHL since infancy. No HA	H_2^{15}O ^{18}F -FDG	Bilateral normal	White noise N-Sig Right Increase, Sig Left Increase	Left CI (N24) Bimodal	3 years 100% disyllables 100% CID sentences
Male, 20 years. Student	Idiopathic perilingual P-SNHL. HA 65% SDS	Idiopathic perilingual P-SNHL. No HA	H_2^{15}O	Bilateral normal	Clicks N-Sig Right Increase, Sig Left Increase	Left CI (N24)	5 years 100% disyllables 70% CID sentences
Male, 46 years. Qualified worker	Perilingual meningitic P-SNHL. Since 16 years. HA 75% SDS	Prelingual meningitic P-SNHL. No HA	H_2^{15}O ^{18}F -FDG	Bilateral normal	White Noise Sig Left Increase	Right CI (N24)	7 years 56% disyllables 78% CID sentences

Note: From "PET study of auditory plasticity: helping to address decision making for cochlear implantation of adults," by F. Cervera-Paz, J. Arbizu, E. Prieto, and M. Manrique, 2009, *Audiological Medicine*, 7, p.52.

In conjunction, auditory rehabilitation programs, including auditory training such as the Listening and Auditory Communication Enhancement (LACE) training program, are based on the ideology that, through individualized training and adaptation via cortical plasticity, patients can improve communicatory efficacy and auditory skills (Sweetow & Henderson-Sabes, 2004). Sweetow and Henderson-Sabes (2004) first examined the effects of individualized auditory training in 8 experienced hearing aid users. The study subjects participated in a month-long training task for 30 minutes a day, five days a week. Four subjects were assigned to the training group, and four subjects to the control group; performance was measured before and following auditory training. Stimuli consisted of digitally recorded sentences in background noise, where the signal-to-noise ratio ranged from -5 to +3 dB. Subjects set their hearing aids to what they considered a comfortable listening level. Three of 4 subjects participating in the training showed improvement on post-training test scores, while none of the subjects in the control group showed any improvement. The authors suggested that, through auditory training programs such as LACE, patients are able to enhance communication and listening skills, resulting in improved peripheral, central and behavioral acclimatization due to cortical plasticity (Henderson-Sabes & Sweetow, 2007; Sweetow & Henderson-Sabes, 2004)

A recent, larger-scale study of the LACE program investigated the efficacy of auditory training on 65 subjects, 56 experienced hearing aid users and 9 subjects who reported difficulty understanding speech in adverse listening environments. Approximately 80% of the research subjects showed overall improvement on LACE tasks, and those subjects with poor initial performances were most likely to demonstrate the greatest overall improvement (Henderson-Sabes & Sweetow, 2007).

Research in the area of tinnitus focuses on the theory that the brain has the potential for change and adaptation, relying on the ideation that the introduction of an acoustic stimulus, or, rather, the abstraction of an acoustic stimulus, can result in eventual sub-cortical and cortical re-organization, or the re-mapping of neural connections (Herraiz, Diges, Cobo, & Aparicio, 2009). Bartels, Staal, and Albers (2007) explored the early and late consequences, or the immediate versus eventual effects, of neural plasticity in relation to auditory deprivation and tinnitus. The authors hypothesized that the early consequences of auditory deprivation, or the abstraction of an acoustic stimulus, may cause dormant or inactive synapses in the central nervous system to become active excitatory nerve synapses. In turn, neuronal information may be re-directed in the central nervous system, creating hyperexcitability, or excessive neuronal activity, throughout the auditory system.

The authors proposed that the late consequences of neural plasticity result in an eventual widespread loss of inhibition due to the aforementioned lateral spread of excitatory responses. Therefore, this proliferation of hyperexcitability may be a mechanism for the perception of tinnitus. In addition, Moller (2006) suggested that this hyperexcitability may produce an abnormal activation of the non-classical auditory pathway as well. The non-classical auditory pathway, associated with the emotional centers of the brain within the limbic system, is suggested to be responsible for the emotional response associated with tinnitus. In turn, the hyperexcitability creates a constant feedback loop between the auditory cortices and limbic system, leading to accompanying symptoms such as depression, anxiety, and phonophobia (Moller, 2006).

The consequences of neural plasticity are explored further when central mechanisms of tinnitus are discussed.

CHAPTER 2

Mechanisms of Tinnitus

Tinnitus is often compared to chronic or phantom pain in that it is typically a subjective experience, often measured by self-report, and usually accompanied by psychological distress. And, like tinnitus, proposed hypotheses for the etiology or mechanisms of chronic pain abound. However, explanatory models for both chronic pain and tinnitus can be divided into two main categories: central and peripheral (Moller, 2000).

In the most basic terms, the peripheral hypothesis of chronic pain postulates that the origin of pain is found at the location of the symptoms, or the site where the patient perceives the pain. Similarly, peripheral hypotheses for tinnitus propose the ear as the sole locus of hyperactivity. Central hypotheses, however, state that modifications within the central nervous system are the cause of chronic pain, and that the location of pathology may be different from where the pain is perceived (Moller, 2000). And, in conjunction, central hypotheses of tinnitus identify numerous areas within the central nervous system that may be responsible or related to the generation of tinnitus.

It is generally accepted that there is not one universal model to explain the etiology or presence of tinnitus in every individual. Thus, it is current belief that

proposed models of tinnitus are not mutually exclusive, but, rather, tools to identify the many possible physiological mechanisms of tinnitus in hopes of establishing correlating treatment methodology.

Peripheral or Cochlear Models

Models that specifically implicate the cochlea or auditory nerve as the consistent and sole source of tinnitus in every patient have been disproven through years of research (Baguley, 2002). For example, tinnitus can develop after the auditory nerve is sectioned and the participation of the cochlea is completely eliminated (Bauer, 2004; Tyler, 2000). Therefore, there is little research to suggest that the generation of tinnitus is purely peripheral, although agreement exists that tinnitus can be induced or triggered by cochlear trauma (Baguley, 2002; Jastreboff, 1990; Saunders, 2007). It is important, then, to review and utilize the knowledge gained from peripheral models in more contemporary and integrative central models.

The discovery of spontaneous otoacoustic emissions in the cochlea was, at one time, hope that tinnitus could be measured objectively. Spontaneous otoacoustic emissions are quantifiable acoustical signals generated by the cochlea in the absence of external stimulation. Researchers suggested there may be a direct relationship between spontaneous otoacoustic emissions and the generation, and frequency, of tinnitus (Tyler, 2000). In turn, several studies examined the use of salicylates as a tinnitus treatment, as spontaneous otoacoustic emissions are often eliminated by the use of aspirin (Long & Tubis, 1988; Penner, 1990; Penner & Coles, 1992). However, these studies have shown that tinnitus and spontaneous otoacoustic emissions are, by and large, independent events,

and treatment with salicylates only improved tinnitus perception in cases where spontaneous otoacoustic emissions and tinnitus were inexorably linked (Penner, 1990; Tyler 2000). Penner (1990) estimated spontaneous otoacoustic emissions as the mechanism for tinnitus in only 4.2% of cases.

It has also been proposed that, following cochlear trauma from noise exposure, an “edge effect” is created by tonotopic regions of normal neuronal activity followed by regions of decreased neuronal activity along the basilar membrane. The reduction in activity of a subpopulation of neurons, perpetuated by increased lateral inhibition, has been suggested as a mechanism for tinnitus. In addition, it has been hypothesized that the pitch of a patient’s tinnitus may correspond with the “edge” or transition point from normal neuronal activity to reduced neuronal activity. However, little empirical evidence exists to support this theory other than patient reports of perceived pitch of tinnitus matching the frequency where normal hearing transitions to elevated pure tone thresholds (Sahley, 2001; Tyler, 2000).

Discordant damage to outer and inner hair cells is the idea that, following cochlear trauma, different areas of outer hair cells will be damaged while areas of inner hair cells will remain intact, and, in turn, render distress on the mechanics of the Organ of Corti. This specific type of damage can occur as a result of noise exposure or ototoxic medication, or from any agent that may cause damage to the basal region of the basilar membrane, with outer hair cells affected first (Jastreboff, 1990).

When the outer hair cells are damaged but inner hair cells remain intact, or fully functional, the tectorial membrane may actually press upon the stereocilia of the inner hair cells as a result of the desynchronization of the tectorial membrane and basilar

membrane. This would then cause the inner hair cells to depolarize, leading to increased auditory afferent activity (Baguley, 2002). In conjunction, it has been theorized that damage to cochlear mechanics may cause an upset in the balance of excitation and inhibition within the cochlea, leading to an increase in endocochlear potential and an enhancement of activity within the auditory nerve (Saunders, 2007). The evidence for the theory of discordant damage to outer and inner hair cells has been demonstrated via protective agents aimed at inhibiting the glutamate's excitatory effect on the auditory nerve fibers, thus functioning as a protective agent against tinnitus (Kaltenbach, 2000).

In conjunction, reduced intracellular calcium concentration and extracellular calcium concentration has been shown to result in burst-firing behavior in the nervous system (Bauer, 2004; Tonndorf, 1981; Tyler, 2000). In turn, it has been hypothesized that changes in calcium concentration within the outer hair cells as well as perilymph may play a role in the generation of tinnitus, as calcium plays an integral role in the transduction process. Jastreboff (1990) hypothesized that decreased calcium in cochlear fluid may not only result in increased burst-firing behavior, but also in the decoupling of the cilia from the tectorial membrane. A reduction in calcium has been shown to cause swelling of the tectorial membrane, and, therefore, an increase in the distance between the cilia and membrane. In turn, partial mechanical decoupling may occur, which may lead to an increase in thermal noise within the auditory system (Bauer, 2004; Jastreboff, 1990; Tonndorf, 1981).

Sahley and Nodar (2001) proposed a biochemical model of peripheral tinnitus, suggesting that endogenous dynorphins, induced by emotional or physical stress, enhance the excitatory properties of glutamate in the cochlea, thereby mimicking the properties of

salicylates and increasing auditory neural discharge. Consequently, this asynchronous activity may be perceived as tinnitus. The authors proposed that this increase in neural discharge may also lead to an increase in neural sensitivity, thereby inducing hyperacusis as well.

Central Models

While peripheral models of tinnitus aim to pinpoint areas within the cochlea that may be responsible for the generation of tinnitus, central theories of tinnitus aspire to identify correlates of tinnitus within the central auditory pathway. Several of these models acknowledge that the primary induction of tinnitus may occur in the auditory periphery, but seek to examine resultant central neuroplastic effects (Muhlnickel, Elbert, Taub, & Flor, 1998). Therefore, central theories seek to differentiate between the ignition site and the resultant mechanisms that advance the perception of tinnitus within the central auditory pathway (Baguley, 2006).

The neurophysiologic model, proposed by Jastreboff (1990), examined not only the cochlear mechanics of tinnitus and changes within the auditory pathway, supported by sub-cortical and cortical auditory centers, but also the psychological principles and perceptual characteristics related to tinnitus. This model, demonstrated in Figure 1, postulates that, although tinnitus may be triggered at the cochlear level, it is developed and processed within the auditory system on several different levels, including connected subsystems (such as the limbic system), and each level serves as a determinant in the patient's tinnitus perception (Jastreboff, 1990; Jastreboff, 1996).

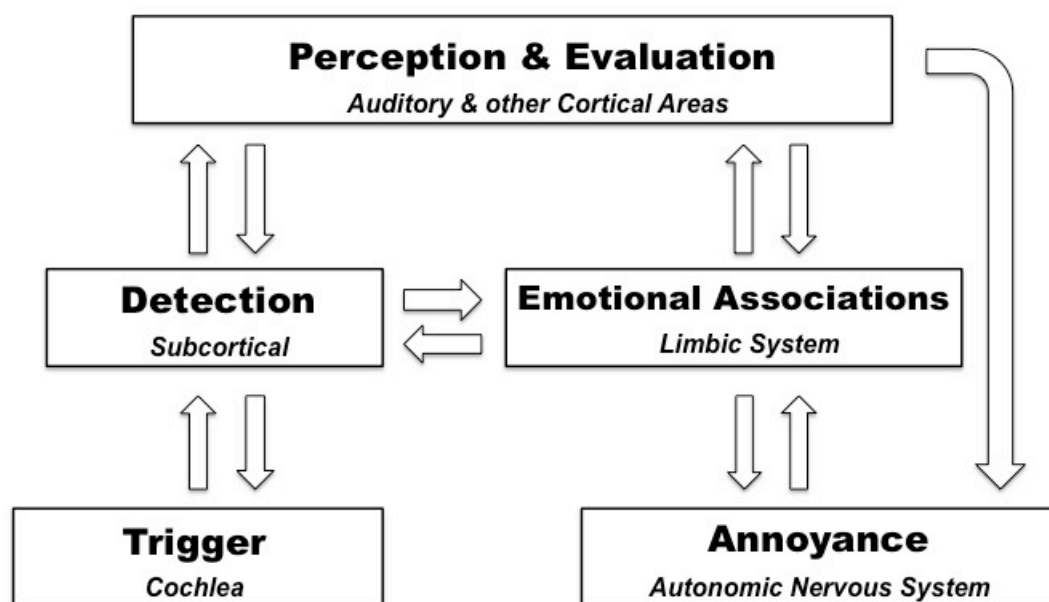


Fig. 1. A block diagram of the stages of tinnitus development and the main centers of the nervous system involved in the emergence of tinnitus perception and in determining its annoyance level. Functional interrelations are described in the text.

Note: From "Neurophysiological Approach to Tinnitus Patients," by P.J. Jastreboff, W.C. Gray and S.L. Gray, 1996, *The American Journal of Otology*, 17, p. 237.

Consequently, the model suggests that there is no passive transmission, as previously hypothesized in early peripheral models (Jastreboff, 1990). In addition, the neurophysiological model acknowledges that the central nervous system is a highly plastic entity, resulting in continuous changes in neural networks. In accordance, the model relies heavily on habituation-based treatment (Jastreboff, Hazell, & Graham, 1994).

Therefore, the neurophysiologic model takes the peripheral theories of the mechanisms of tinnitus several steps further. Jastreboff (1990, 2007) proposed hyperactivity originating in the auditory periphery, specifically as a result of discordant damage to outer and inner hair cells, as a possible mechanism for tinnitus. He hypothesized that the resulting disruption of inhibition and excitation within the classical

auditory pathway and non-classical auditory pathway may result in continual and long-term changes in neural networking. Subsequently, the neurophysiologic model postulates that non-auditory systems, such as the limbic and autonomic nervous system, have a dominating role in the severity of the patient's tinnitus.

At the detection level of the neurophysiologic model, Jastreboff (2000) suggests that neural assemblies enhance or differentiate the signal (tinnitus) from spontaneous activity due to newness and repetition. The signal then becomes reinforced through emotional association, or the alarm and fear the tinnitus may trigger within the patient. In essence, neural assemblies become perpetually tuned to the tinnitus signal, and the level of the patient's annoyance may continually increase (Jastreboff, 2007).

Within the confines of the neurophysiological model, the input of additional subsystems, specifically the limbic system, within the central nervous system cannot be underestimated. The emotions attached to the perception of tinnitus enhance the attention invested in the tinnitus. Increased attention is then accompanied by increased detection, and strengthened by long- and short-term memory. In addition, the pre-frontal cortex has been pinpointed as a possible integrative structure for both the sensory and emotional factors associated with tinnitus. Therefore, this specific cortical area may reinforce and bolster the perception and negative emotions associated with tinnitus, creating a continuous feedback loop focusing the nervous system on the perception of the tinnitus (Jastreboff, 2000; Jastreboff, 2007).

Recent research in support of central theories have focused on obtaining concrete evidence for the plastic changes, including the induction of inhibition and excitation, within the central auditory pathway, through animal research. In addition, many studies

have directed attention to examining specific areas within the auditory pathway in hopes of identifying an initial trigger, modulative or integrative region for the perception of tinnitus.

Salvi, Wang, and Ding (2000) confirmed functional changes in the central auditory pathway of chinchillas after the cochlea was damaged as a result of acoustic overstimulation and carboplatin. Electrodes were implanted on the round window of the cochlea or in the cochlear nucleus, inferior colliculus or the auditory cortex of chinchillas. Baseline neural activity was obtained from neurons before cochlear trauma was induced. Enhanced neural activity, specifically in the dorsal cochlear nucleus and inferior colliculus, following exposure suggested central compensation for changes in neural activity of the periphery. This research suggested that deafferentation of the cochlea may lead to neural reorganization, and, in turn, centrally induce the perception of tinnitus.

Additional research has also served to implicate the dorsal cochlear nucleus and inferior colliculus as significant sites in the etiology and modulation of tinnitus. Kaltenbach (2000) investigated activity in the dorsal cochlear nucleus of rats one month following exposure to intense sound (125-130 dB) for four hours. Results showed the rats had significant hyperactivity in the dorsal cochlear nucleus, which continued to increase over subsequent months post-treatment. It has been hypothesized that the onset of hyperactivity found in cochlear-insult animal models suggests the loss of lateral inhibition throughout the entirety of the central auditory system, and may give insight into the cause and effect relationships liable for tinnitus (Salvi, 2000; Kaltenbach, 2000).

Brozoski and Bauer (2005) attempted to examine the effects of dorsal cochlear nucleus ablation on acoustic trauma-induced tinnitus in rats. The researchers hypothesized that ablation would decrease psychophysical evidence for tinnitus, and, in turn, isolate the dorsal cochlear as a possible generator of tinnitus. However, the authors found that bilateral ablation of the dorsal cochlear nucleus in rats did not, in fact, reveal psychophysical evidence for tinnitus. Moreover, ablation of the bilateral dorsal cochlear nuclei had no significant effect on psychophysical evidence tinnitus. Ipsilateral ablation, however, provided increased psychophysical evidence for tinnitus. This evidence indicated that the dorsal cochlear nucleus may not necessarily serve as a simple “feed forward generator” for chronic trauma- induced tinnitus. The authors also suggested that the output of the dorsal cochlear nucleus following acoustic trauma may trigger permanent tinnitus-related afferent neural activity that cannot be terminated by subsequent ablation. Therefore, the dorsal cochlear nucleus may play a role in the generation of tinnitus, but not in the persistence of tinnitus.

Eggermont (2005) examined tinnitus perception in relation to the auditory cortex. Changes in the tonotopic map of the primary auditory cortex following acoustic trauma has been well documented. The caudal to rostral tonotopic organization of the auditory cortex is analogous to place coding in the cochlea. However, after intense noise exposure, cortical neurons, which once responded to the characteristic frequency of the damaged frequency region, instead respond to the frequency tuning of less affected frequency regions. In turn, increased spontaneous firing activity and neural synchrony occurs in the affected frequency regions. It is speculated that these changes upset the balance of

excitation and inhibition (glutamate and GABA) in the auditory pathway and may contribute to the perception of tinnitus.

Additionally, in some cases, tinnitus can be modulated through somatic manipulations, or altered by cross-modal interactions. For example, perception of loudness, pitch or location of tinnitus can be altered through craniocervical manipulations, such as contractions of the neck or shoulder, or oro-facial maneuvers, such as clenching of the jaw. It has been hypothesized that the ability to alter the perception of tinnitus somatically is a result of the interaction of somatosensory pathways suggests sensory integration in a central location (Kaltenbach et al., 2005). For example, Lockwood et al. (1998) studied patients where the loudness of tinnitus was altered by jaw clenching. The authors found that, when the patients clenched their jaws, increases and decreases in cerebral blood flow, measured by PET, occurred in the medial geniculate body as well as the auditory cortex and hippocampus.

Hyperacusis is a common and distressing accompanying condition to severe tinnitus. (Tyler, 2000). In fact, Jastreboff et al. (1996) found that approximately 40 percent of patients who complained of tinnitus also experienced hyperacusis. And, although there is a lack of empirical evidence suggesting a definitive connection between tinnitus and hyperacusis, proponents of the neurophysiological or central models of tinnitus suggest that the two conditions are inexorably linked. In turn, current research has focused on modifications to a hypothetical compensatory gain mechanism of the central auditory pathway, or central regulation of supra-threshold sensitivity, that may be triggered by the same hyperactivity within the auditory system that many specify as a

mechanism for tinnitus (Baguley, 2003; Formby, Sherlock, & Gold, 2003; Moller, 2006; Tyler 2000).

Formby et al. (2003) examined sound therapy, or the process of desensitization to sound by prolonged exposure to an enriched sonic background, in relation to disturbances in the compensatory gain process of the central auditory pathway, or the central regulation of supra-threshold sensitivity, of subjects with normal hearing and normal loudness perception. Eight participants were fit with bilateral earplugs (auditory deprivation group) while 7 participants were fit with bilateral ear-level devices (General Hearing Instruments, Tranquil model) constantly emitting a low-intensity noise (auditory enrichment group). The noise produced by the device ranged between approximately 1000 and 8000 Hz, with a peak level of approximately 50 dB SPL at 6000 Hz. Participants in each condition wore their respective ear-level devices for 23 hours a day over a two-week treatment period. Results revealed significant shifts in loudness judgment, as shown by the Contour Loudness Perception Test (CLPT). Utilizing the CLPT, subjects assigned a series of tones to one of seven levels of perceived loudness, ranging from very soft to uncomfortably loud. The auditory deprivation group required significantly (5-9 dB) less intense tones in judgment of comfort and loudness, while the auditory enhancement group required significantly (4-8 dB) louder tones in judgment of comfort and loudness.

A modified version of Tinnitus Retraining Therapy, a tinnitus treatment method based on habituation, further explored when tinnitus treatment is discussed, has also been proposed for the treatment of hyperacusis (Jastreboff & Jastreboff, 2000). Sound therapy, utilizing ear-level wide-band sound generators along with directive counseling targeting

patient distress, has been suggested as a method of gradually desensitizing the hyperacusic patient to the intensity of sound (Baguley, 2003; Jastreboff & Jastreboff, 2000). This type of treatment of hyperacusis is based on the assumption that the supra-threshold sensitivity, and, specifically, the central gain mechanism, of the auditory system can be modified. In turn, those who propose a central link between tinnitus and hyperacusis also suggest that sound therapy may be utilized as tool to modify the perceptual characteristics of tinnitus as well (Formby et al, 2003; Jastreboff & Jastreboff, 2000). And, although little research has been published examining the success of utilizing retraining therapy for the treatment of hyperacusis, observational studies have suggested improvements in loudness discomfort levels (Baguley, 2003).

CHAPTER 3

Tinnitus Treatment

Although a significant amount of research has been conducted, there is still not one universally accepted model or mechanism for the generation of the perception of tinnitus. In conjunction, there is not one universally accepted treatment methodology. However, there are several interventions that address both the physiological and psychological aspects of tinnitus within a neuroplastic framework.

Hearing Aids and Masking Devices

Tinnitus maskers, whether hearing aids (amplification), sound generators, or combination instruments (amplification accompanied by a sound generator), are meant to reduce the patient's perception of tinnitus loudness. Additionally, maskers may help to change the pitch of the patient's tinnitus, making it less distressing or unsettling (Henry et al., 2006).

Del Bo and Ambrosetti (2007) examined hearing aids as a tinnitus treatment option. The authors not only reported that amplifying ambient noise allowed for tinnitus to gradually become less intrusive and attention-worthy, but also hypothesized that the introduction of new auditory stimuli may trigger central reorganization. In congruence,

several studies have shown hearing aids and maskers to improve the patient's perception of tinnitus and its associated level of aggravation (Del Bo & Ambrosetti, 2007; Tyler, 2000).

Folmer and Carroll (2006) examined the effectiveness of hearing aids and ear-level sound generators as treatment options for tinnitus. Hearing aids utilized in the study were categorized as current digital technology while the ear-level sound generators had a maximum output of 77 dB SPL and produced a broadband response (100-8000 Hz). Following treatment, 70% of hearing aid users experienced improvements in tinnitus, and 76% of those using sound generators experienced improvements in tinnitus as measured by the Tinnitus Severity Index (TSI), a subjective outcome measure aimed at measuring the negative impact of tinnitus on the patient's life. Specifically, hearing aids users who had improved sleep patterns experienced a 23% reduction in TSI scores, and sound generator users experienced a 17% reduction in TSI scores.

Additionally, a 2009 study investigating the effects of hearing aids on tinnitus revealed that low-medium (low to medium ends of the human audible spectrum) spectra amplification produced significant changes in low frequency components of tinnitus perception over a one-month period. It was suggested that a longer treatment time period may lead to changes in the high frequency components of the tinnitus spectra as well. The authors postulated that hearing aids could restore afferent input into the auditory system as a whole, adjusting or disrupting the properties of tinnitus generation within the patient's neural network, thereby integrating the fundamentals of neural plasticity (Moffat et al., 2009).

Tinnitus Retraining Therapy

One of the most common treatments for tinnitus is tinnitus retraining therapy (TRT), based on the concept of habituation. The therapy implies that several subsystems within the central nervous system are involved in the development of tinnitus and its associated level of aggravation (Jastreboff, Gray, & Gold, 1996; Seidman, Standring, & Dornhoffer, 2010). Therefore, this specific model is dependent on Jastreboff's neurophysiological model and the fundamentals of neural plasticity, specifically that the central nervous system has the capacity to adjust and eventually adapt to neutral signals (Henry et al., 2006; Jastreboff et al., 1996).

TRT acknowledges the limbic system and the autonomic nervous system as key contributors in the level of the patient's perception of tinnitus. The treatment method is based on the assumption that an originally weak, peripheral signal may reach higher cortical areas and be perceived as tinnitus. Consequently, the limbic system is activated when a negative emotional reaction is attached to the tinnitus, also inducing activation of the autonomic nervous system in preparation for what may be perceived as danger or threat. Thus, the perception of tinnitus is enhanced through continual negative reinforcement, preventing the patient from eventually habituating to the signal (Henry et al., 2005; Jastreboff et al., 1996).

Therefore, TRT is an integrative treatment methodology involving directive counseling of the patient as well as sound therapy (Jastreboff et al., 1994; Seidman et al., 2010). The purpose of directive counseling is to educate the patient as to current knowledge about tinnitus generation and perception as well as the physiology of hearing

and attached processes. This edification is an attempt to remove or disassociate the negative emotional response from the tinnitus, making phantom auditory perception non-threatening and void of detrimental influence (Jastreboff et al., 1994; Henry et al., 2005). Sound therapy is also employed to in TRT, utilizing amplification or ear-level sound generators to facilitate habituation. The difference between background neuronal activity and the neuronal activity of the tinnitus is decreased when amplification or additional noise is introduced (McKenna, 2004). Ultimately, the goal of the sound therapy is not to mask, but to make the process of detecting the tinnitus from the background noise difficult, relying on the fundamental ability of the nervous system to adjust neural connections and adapt (Henry et al., 2006; Jastreboff et al., 1996; Jastreboff, 2007; McKenna, 2004).

Henry et al. (2006) examined the outcome measures of clinical trials utilizing TRT accompanied by tinnitus masking (TRT) versus tinnitus masking only (TM) over an eighteen-month period. Masking administered in the TRT treatment method utilized any brand or model of hearing aid, ear-level sound generator or combination device that met performance criteria for TRT; standards included stability of wideband noise, open-ear configuration, and precision volume adjustment at low levels. The TRT method also employed structured educational counseling to demystify tinnitus as well as address and eliminate negative emotions associated with tinnitus. Masking for the TM method utilized any model or brand of hearing aid, ear-level sound generator, or combination device that provided relief from tinnitus through complete or partial masking. Counseling in the TM method was limited to informal education regarding the use of

sound therapy for tinnitus relief, methods for reducing stress, and alleviating worry regarding long-term effects of tinnitus.

The authors found that, while both groups showed declines from baseline measures in tinnitus handicap and severity as measured by the Tinnitus Handicap Questionnaire (THQ), Tinnitus Handicap Inventory (THI), and Tinnitus Severity Index questionnaires (TSI), the decline was significantly greater in those treated with TRT, specifically for those who had a considerable tinnitus problem at the beginning of the study. Scores for those receiving TRT exhibited average declines of -15.8, -14.7, and -6.2 points on the THI, THQ and TSI, respectively, while scores declined an average of -4.5, -2.2, and -1.2 points for those given the TM treatment. Figure 2 demonstrates the significant decline in THI scores for those in the TRT group where tinnitus was deemed a “very big problem” as compared to those in the TM group who identified tinnitus as a “very big problem” (Henry, 2006).

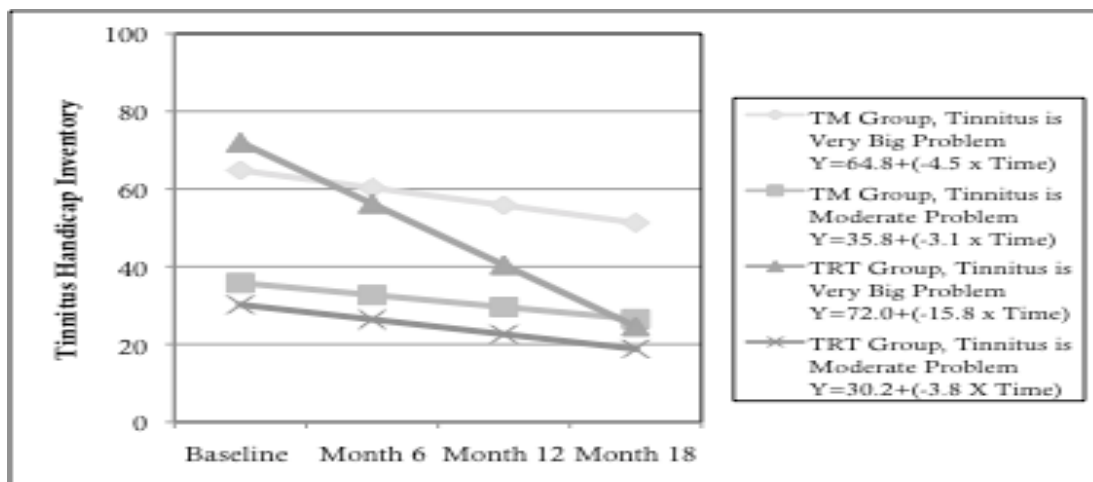


Figure 1. Treatment X tinnitus problem interaction for the THI outcome. Shown are four THI trajectories across 18 months. Two trajectories are for TM patients who began treatment with either a very big or a moderate tinnitus problem; the other two trajectories are for TRT patients who began treatment with either a very big or a moderate tinnitus problem. Hearing loss and duration of tinnitus are controlled for, with trajectories computed for patients with average hearing loss ($z=0$) and the median duration of tinnitus (11 to 20 years, coded as 0).

Note: From "Outcomes of Clinical Trial: Tinnitus Masking versus Tinnitus Retraining Therapy," by J. Henry, M. Schechter, T. Zaugg, S. Griest, P. Jastreboff, J. Vernon, and B. Stewart, *The Journal of the American Academy of Audiology*, 17, p. 121.

Neuromonics

Neuromonics is a tinnitus treatment aimed at treating the auditory, attentional and emotional facets of tinnitus through a six-month rehabilitation program relying on systemic desensitization. Highly customized broadband musical stimuli, created specifically for the patient's hearing and tinnitus characteristics, are utilized at crucial distress moments to intermittently mask the tinnitus, providing the patient with a sense of relief, relaxation and control. In conjunction, a structured rehabilitation program is followed to educate the patient about tinnitus, address any cognitive distortions regarding tinnitus, coach and modify behaviors in relation to sleep, relaxation and the reduction of stress, and counsel the patient regarding the emotional response attached to the tinnitus. The program monitors progress of the patient, setting treatment goals customized to the unique needs of each patient (Davis, Paki, & Hanley, 2007; Hanley & Davis, 2008). The Neuromonics treatment is rooted in the principles of neural plasticity, depending on the theory that the limbic system and autonomic system play a large role in tinnitus-related disturbances. The contributions of these systems lead to further tinnitus awareness and loudness, a cycle that sustains tinnitus perception and can cause tinnitus to become progressively worse. In addition, Neuromonics may also be utilized as a treatment for hyperacusis, a condition often associated tinnitus. It has been proposed that increased or high gain within the auditory system, limbic system, and autonomic systems, as a result of tinnitus, may reduce the patient's tolerance of loud auditory stimuli (Hanley & Davis, 2008; Jastreboff & Jastreboff, 2000)

Davis et al. (2007) examined the effect of the Neuromonics treatment on 34 patients with clinically significant tinnitus. The authors primarily measured improvement

in the perception of tinnitus using the Tinnitus Reaction Questionnaire (TRQ), with a threshold of 40% improvement deemed clinically significant to ensure evident progress from the patient's perspective. At six months into treatment, 91% of all patients had achieved at least 40% improvement on the TRQ, and 80% of patients reported a level of tinnitus disturbance that was no longer clinically significant. In addition, a significant improvement in the tolerance of loud sounds, measured by loudness discomfort levels, was noted (Davis et al., 2007).

Moreover, the use of tailor-made music, or music filtered to remove energy in the frequency range centered around the individual's tinnitus frequency, has shown promise as a tonal tinnitus treatment. Okamoto, Stracke, Stoll, and Pantev (2010) examined a one-year course of customized music treatment on a group of 23 patients who experienced chronic, tonal tinnitus. Results showed that the customized music treatment significantly reduced subjective tinnitus loudness perception as measured by a continuous visual analog scale ranging from 0 (no tinnitus) to 100 (extremely loud tinnitus) after only six months. The authors suggested that deprivation of auditory input surrounding the tinnitus frequency may have triggered functional deafferentation or inhibition of auditory neurons corresponding to the tinnitus frequency, and, therefore, a neuroplastic effect within the auditory system.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT), often used as a treatment for chronic pain, has been suggested as a viable method for the treatment of tinnitus. This specific kind of therapy aims to change the learned and maladaptive behaviors and thought- patterns of

the patient through intensive therapy, and is based on the assumption that the cortical systems involved in the perception of a chronic condition, such as tinnitus or pain, can be molded to de-emphasize the significance of the condition (Sweetow, 1986; Sweetow & Sabes, 2010; Tyler, 2000). In turn, the ultimate goal of the therapy is to make the chronic condition a neutral aspect of the patient's life (Sweetow, 1986).

Turner et al. (2006) examined the use of CBT as a treatment method for those with chronic temporomandibular disorder (TMD) pain. Research subjects were assigned to four sessions of CBT or four sessions of self-care management (SCM), which solely focused on general education regarding health-care. Twelve months following initial treatment, subjects who had participated in CBT displayed statistically significant long-term improvement on subjective questionnaires examining pain perception, depression, overall jaw function and the effect of TMD pain on daily activities.

In turn, Sweetow (1986) reported significant improvement in tinnitus loudness and annoyance functions for two case studies following cognitive-behavioral therapy intervention, spurring further research for CBT, in conjunction with sound therapy, as a treatment method for tinnitus (Sweetow, 1986; Sweetow and Sabes, 2010)

Jakes et al. (1992) studied the effects of group cognitive therapy versus a placebo masker therapy, where the masker emitted a low-level broadband noise. The use of the group cognitive therapy alone was not statistically more effective than the placebo masker group. However, the combined use of masking plus group cognitive therapy showed a significant improvement in the patients' emotional distress and auditory-perceptual difficulties.

Henry and Wilson (1999) examined the effects of CBT intervention on 103 patients with moderate to severe tinnitus. This study employed highly trained CBT therapists, utilized a highly structured treatment manual, encouraged focus on homework assignments, and allowed for written and audiotaped materials to complement the therapy sessions. The CBT participants displayed significant reductions in scores of tinnitus-related psychological distress on the TRQ.

Pharmacologic Intervention

When the symptoms of tinnitus extend beyond the realm audiological treatment and behavioral counseling, pharmacologic intervention may be necessary. Insomnia, severe anxiety and depression, obsessive thinking and agitation are symptoms that may accompany tinnitus (Centore, 2010). Although several studies have been conducted to inspect the efficacy of pharmacologic agents on tinnitus, results have varied. It has been theorized that many mechanisms underlie tinnitus perception, and, therefore, it cannot be treated as a homogenous disorder. In fact, Bauer and Brozoski (2008) suggested that a stratified study design which categorizes tinnitus by type, etiology and hearing characteristics would be more successful in determining which pharmacologic treatments may be successful.

Enhanced neural activity and loss of inhibition as a mechanism of tinnitus is the theory underlying the use of drugs like lidocaine and anti-epileptics. These medications serve as neural stabilizers to restore inhibitory control, thus attempting to reduce or eliminate the perception of tinnitus (Bauer & Brozoski, 2006). A 2005 study examined the effects of intravenous lidocaine treatment on tinnitus. While 23.3% of the patients

treated experiences partial or full suppression of tinnitus immediately, only 3.3% experienced any suppression four weeks post-treatment (Kalcioğlu, Bayindir, Erdem, & Özturan, 2005).

Antidepressants, as well as anti-anxiety medications, are commonly utilized in the management of the emotional symptoms of chronic tinnitus. It has been hypothesized that the pharmacological effect of these medications may involve neurotransmitters and receptors within the auditory pathway (Bauer & Brozoski, 2006). A recent study examined the effects of Sertraline (Zoloft) on tinnitus patients using the Tinnitus Severity Questionnaire (TSQ) as a primary outcome measure. Outcome analysis showed Sertraline to be effective in comparison to a placebo treatment, with improvements in anxiety and depression linked to a reduction in tinnitus perception on the TSQ (Zolger et al., 2006).

Anti-insomnia agents, such as benzodiazepines, are effective in promoting healthy sleep for the tinnitus patient in the short-term. By enhancing the action of GABA in the nervous system, this type of medication causes sedation through inhibition (Centore, 2010). In addition, benzodiazepines may serve to relieve some of the agitation and anxiety that can result from tinnitus-related sleep deprivation. A 1993 study of the effect of Alprazolam (Xanax) on tinnitus showed that 76% of the treatment group reported improvements in subjective and objective tinnitus compared to only 5% of the placebo group (Johnson et al., 1993).

However, while pharmacologic intervention may often prove beneficial, it is imperative to consider that tinnitus is currently reported as a side effect of many of the

medications that can also serve to alleviate symptoms, and, therefore, could result in the patient's perceived worsening of tinnitus (Robinson, 2007).

Repetitive Transcranial Magnetic Stimulation

As research has pointed to a neurobiological abnormality as a possible mechanism for chronic tinnitus, a recent treatment has emerged to stimulate the brain so as to reduce neural activity. Repetitive transcranial magnetic stimulation (rTMS), a non-invasive treatment method where brief low- frequency magnetic pulses are delivered via magnetic coil through the scalp and skull, has been shown to modify cortical activity by inducing depolarization of cells in the brain underlying stimulation (Kleinjung, Steffens, Londero, & Langguth, 2007). It has been suggested that repeatedly stimulating the hyperactive auditory cortex via rTMS, and thereby modifying cortical excitability, may interrupt the perception of disabling tinnitus by inducing neural plasticity in cortical circuits and thalamocortical networks (Eichhammer, Kleinjung, Landgrebe, Hajak, & Langguth, 2007; Kleinjung et al., 2007; Seidman et al., 2010).

Eichhammer et al. (2007) scrutinized the effects of low frequency rTMS when applied over the auditory cortex of 36 healthy patients without tinnitus. The results of the study revealed that rTMS did induce a cortical silent period (CSP), or interruption of tinnitus perception, in the treatment group, as opposed to the placebo rTMS treatment group where no CSP was observed. Therefore, inhibition within the auditory cortex was induced via stimulation, although results were not permanent. A 2008 case study of the effect of rTMS showed a significant reduction in tinnitus loudness after three rounds, or

maintenance sessions, of rTMS, suggesting that this treatment may be a future avenue to explore for the treatment of tinnitus (Mennemeier et al., 2008).

CHAPTER 5

The Future of Tinnitus

Although progress has been made throughout years of investigation, the mechanisms of tinnitus continue to elude us. The complexity of collecting empirical evidence for the generation of a condition that is both subjective and linked to numerous neurological substrates is daunting. However, it is evident that the future of research in the arena of tinnitus must be rooted in carefully controlled research providing the highest levels of evidence (Tyler, 2000). Specifically, there is a paucity of systematic reviews, randomized controlled trials and cohort studies to support deductions or assumptions regarding the mechanisms for tinnitus, and the relationship of tinnitus perception with treatment methodology and neural plasticity.

However, in reviewing the current research, it is apparent that progress has been made and is forthcoming, and the idea of neural plasticity, specifically that the activity of the brain can be molded to suspend maladaptive behavior, is a guiding force. Further investigation into hyperactivity within specified regions of the auditory pathway, and the interaction of the peripheral and central auditory system, as well as the role of the limbic system, is integral in providing more guidance for exploring the mechanisms of tinnitus as well as neural plasticity in treatment methodology. In addition, research utilizing PET,

functional Magnetic Resonance Imaging, and other relatively objective outcome measures is suggested to establish empirical evidence.

Furthermore, exploring the features of neural plasticity in the human auditory system may be beneficial to the advancement of treatment options. For example, investigating the permanency of plastic changes, such as variables factoring into the extent and time course of plasticity, as well as measuring the relationship between physiological changes and perceptual changes, may give insight into the wide variability of adaptation and acclimatization effects (Willott, 1996).

In conclusion, the success of various tinnitus treatments, such as Neuromonics, rTMS and CBT, shows promise for those who are currently experiencing chronic tinnitus. It is evident that there is, and may never be, a one-size-fits-all treatment. However, with the help of an interdisciplinary collaboration between audiology, otology, pharmacology, neurology and psychology, and the knowledge of the neuroplastic elements of the human auditory system, tinnitus is more treatable today than it ever has been (Baguley, Davies, & Hazell, 2003).

LIST OF REFERENCES

- Baguley, D. M. (2002). Mechanisms of tinnitus. *British Medical Bulletin*, 63, 195-212.
- Baguley, D. M. (2003). Hyperacusis. *Journal of the Royal Society of Medicine*, 96(12), 582-585.
- Baguley, D. M. (2006). Tinnitus: recent insights into mechanisms, models, and therapies. *The Hearing Journal*, 59(5), 10-15.
- Baguley, D. M., Davies, E., & Hazell, J. (2003). A vision for tinnitus research. *International Journal of Audiology*, 42, 2-3.
- Bartels, H., Staal, M. J., & Albers, F. (2007). Tinnitus and Neural Plasticity of the Brain. *Otology & Neurotology*, 28, 178-184.
- Bauer, C. A. (2004). Mechanisms of tinnitus generation. *Current Opinion in Otolaryngology & Head and Neck Surgery*, 12, 413-417.
- Bauer, C. A., & Brozoski, T. J. (2006). Tinnitus Assessment and Treatment: Integrating Clinical Experience with the Basic Science of Tinnitus. *Seminars in Hearing*, 29(4), 371-385.
- Brozoski, T. J., Bauer, C. A., & Caspary, D. M. (2005). The effects of dorsal cochlear nucleus ablation on tinnitus in rats. *Hearing Research*, 206, 227-236.
- Centore, L. S. (2010). A guide to pharmacologic management of target symptoms of severe tinnitus. *The Hearing Journal*, 63(11), 36-42.
- Cervera-Paz, F., Arbizu, J., Prieto, E., & Manrique, M. (2009). PET study of auditory plasticity: helping to address decision making for cochlear implantation of adults. *Audiological Medicine*, 7(1), 47-54.
- Davis, P. B., Paki, B., & Hanley, P. J. (2007). Neuromonics Tinnitus Treatment: Third Clinical Trial. *Ear & Hearing*, 28(2), 242-259.
- Del Bo, L., & Ambrosetti, U. (2007). Hearing aids for the treatment of tinnitus. *Progress in Brain Research*, 166, 341-345.
- Eggermont, J. J. (2005). Tinnitus: neurobiological substrates. *Drug Discovery Today*, 10(19), 1283-1290.

- Eichhammer, P., Kleinjung, T., Landgrebe, M., Hajak, G., & Langguth, B. (2007). TMS for treatment of chronic tinnitus - neurobiological effects. *Progress in Brain Research*, 166, 369-374.
- Folmer, R. L., & Carroll, J. R. (2006). Long-Term Effectiveness of Ear-Level Devices for Tinnitus. *Otolaryngology-Head and Neck Surgery*, 134, 132-137.
- Formby, C., Sherlock, L. P., & Gold, S. L. (2003). Adaptive plasticity of loudness induced by chronic attenuation and enhancement of the acoustic background. *The Journal of the Acoustical Society of America*, 114(1), 55-58.
- Hanley, P. J., & Davis, P. B. (2008). Treatment of Tinnitus With a Customized, Dynamic, Acoustic Neural Stimulus: Underlying Principles and Clinical Efficacy. *Trends in Amplification*, 12(3), 210-222.
- Henderson-Sabes, J., & Sweetow, R. W. (2007). Variables predicting outcomes on listening and communication enhancement (LACE) training. *International Journal of Audiology*, 46, 374-383.
- Henry, J., & Wilson, P. (1999). Cognitive-behavioural therapy for tinnitus-related distress: An experimental evaluation of initial treatment and relapse prevention. *Sixth International Tinnitus Seminar*.
- Henry, J. A., Dennis, K. C., & Schechter, M. A. (2005). *Journal of Speech, Language, and Hearing Research*, 48, 1204-1235.
- Henry, J. A., Schechter, M. A., Loovis, C. L., Zaugg, T. L., Kaelin, C., & Montero, M. (2005). Clinical management of tinnitus using a "progressive intervention" approach. *Journal of Rehabilitation Research & Development*, 42(4), 95-116.
- Henry, J. A., Schechter, M. A., Zaugg, T. L., Griest, S., Jastreboff, P. J., Vernon, J. A., Stewart, B. J. (2006). Outcomes of Clinical Trial: Tinnitus Masking versus Tinnitus Retraining Therapy. *The Journal of the American Academy of Audiology*, 17, 104-132.
- Herraiz, C., Diges, L., Cobo, P., & Aparicio, J. M. (2009). Cortical reorganisation and tinnitus: principles of auditory discrimination training for tinnitus management. *European Archives of Oto-Rhino-Laryngology*, 266, 9-16.
- Jakes, S. C., Gakkan, R. S., McKenna, L., & Hinchcliffe, R. (1992). Group Cognitive Therapy for Medical Patients: An Application to Tinnitus. *Cognitive Therapy and Research*, 16(1), 67-82.
- Jastreboff, M. M. (2007). Sound therapies for tinnitus management. *Progress in Brain Research*, 166, 435-440.

- Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): mechanisms of generation and perception. *Neuroscience Research*, 8, 221-254.
- Jastreboff, P. J. (2007). Tinnitus retraining therapy. *Progress in Brain Research*, 166, 415-423.
- Jastreboff, P. J., & Jastreboff, M. M. (2000). Tinnitus Retraining Therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. *Journal of the American Academy of Audiology*, 11, 162-177.
- Jastreboff, P. J., Gray, W. C., & Gold, S. L. (1996). Neurophysiological Approach to Tinnitus Patients. *The American Journal of Otology*, 17, 236-240.
- Jastreboff, P. J., Hazell, J., & Graham, R. L. (1994). Neurophysiological model of tinnitus: Dependence of the minimal masking level on treatment outcome. *Hearing Research*, 80, 216-232.
- Johnson, R., Brummett, R., & Schleuning, A. (1993). Use of alprazolam for relief of tinnitus: A double-blind study. *Archives of Otolaryngology - Head and Neck Surgery*, 119(8), 842-845.
- Kalcioglu, M. T., Bayindir, T., Erdem, T., & Ozturan, O. (2005). Objective evaluation of the effects of intravenous lidocaine on tinnitus. *Hearing Research*, 199, 81-88.
- Kaltenbach, J. A. (2000). Neurophysiologic Mechanisms of Tinnitus. *The Journal of the American Academy of Audiology*, 11(3), 125-137.
- Kaltenbach, J. A., Zhang, J., & Finlayson, P. (2005). Tinnitus as a plastic phenomenon and its possible neural underpinnings in the dorsal cochlear nucleus. *Hearing Research*, 206, 200-226.
- Kennedy, V., Wilson, C., & Stephens, D. (2004). Quality of Life and Tinnitus. *Audiological Medicine*, 2, 29-40.
- Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' - a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, 28(1), 76-81.
- Kleinjung, T., Steffens, T., Londero, A., & Langguth, B. (2007). Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. *Progress in Brain Research*, 166, 359-367.
- Kral, A., & Majernik, V. (1996). On Lateral Inhibition in the Auditory System. *General Physiology and Biophysics*, 15, 109-127.

- Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. *Neurology*, *50*, 114-120.
- Long, G., & Tubis, A. (1988). Modification of spontaneous and evoked emissions and associated psychoacoustic microstructure by aspirin consumption. *Journal of the Acoustical Society of America*, *84*, 1343-1353.
- Martines, F., Bentivegna, D., Martines, E., Sciacca, V., & Martinciglio, G. (2010). Characteristics of tinnitus with or without hearing loss: Clinical observations in Sicilian tinnitus patients. *Auris Nasus Larynx*, *37*, 685-693.
- McKenna, L. (2004). Models of Tinnitus Suffering and Treatment Compared and Contrasted. *Audiological Medicine*, *2*, 41-53.
- Mennemeier, M., Chelette, K. C., Myhill, J., Taylor-Cooke, P., Bartel, T., Triggs, W., ... Dornhoffer, J. (2008). Maintenance Repetitive Transcranial Magnetic Stimulation Can Inhibit the Return of Tinnitus. *The Laryngoscope*, *118*, 1-5.
- Moffat, G., Adjout, K., Gallego, S., Thai-Van, H., Collet, L., & Norena, A. J. (2009). Effects of hearing aid fitting on perceptual characteristics of tinnitus. *Hearing Research*, *254*, 82-91.
- Moller, A. R. (2000). Similarities between Severe Tinnitus and Chronic Pain. *Journal of the American Academy of Audiology*, *11*(3), 115-124.
- Moller, A. R. (2006). Neural plasticity in tinnitus. *Progress in Brain Research*, *157*, 365-372.
- Muhlnickel, W., Elbert, T., Taub, E., & Flor, H. (1998). Reorganization of the auditory cortex in tinnitus. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(17), 1340-1343.
- Munro, K. J., Walker, A. J., & Purdy, S. C. (2007). Evidence for adaptive plasticity in elderly monaural hearing aid users. *Neuroreport*, *18*(12), 1237-1240.
- Okamoto, H., Stracke, H., Stoll, W., & Pantev, C. (2010). Listening to tailor-made notched music reduces tinnitus loudness and tinnitus-related auditory cortex activity. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(3), 1207-1210.
- Penner, M., & Coles, R. (1992). Indications for aspirin as a palliative for tinnitus caused by SOAEs: a case study. *British Journal of Audiology*, *26*, 91-96.
- Penner, M. J. (1990). An estimate of the prevalence of tinnitus caused by spontaneous

- otoacoustic emissions. *Archives of otolaryngology--head & neck surgery*, 116(4), 418-423.
- Robinson, S. (2007). Antidepressants for treatment of tinnitus. *Progress in Brain Research*, 166, 263-271.
- Sahley, T. L., & Nodar, R. H. (2001). A biochemical model of peripheral tinnitus. *Hearing Research*, 152, 43-54.
- Salvi, R. J., Wang, J., & Ding, D. (2000). Auditory plasticity and hyperactivity following cochlear damage. *Hearing Research*, 147, 261-274.
- Saunders, J. C. (2007). The role of central nervous system plasticity in tinnitus. *Journal of Communication Disorders*, 40, 313-334.
- Seidman, M. D., Standring, R. T., & Dornhoffer, J. L. (2010). Tinnitus: current understanding and contemporary management. *Current Opinion in Otolaryngology & Head and Neck Surgery*, 18, 363-368.
- Shargorodsky, J., Curhan, G. C., & Farwell, W. R. (2010). Prevalence and Characteristics of Tinnitus among US Adults. *The American Journal of Medicine*, 123(8), 711-718.
- Sweetow, R. W. (1986). Cognitive Aspects of Tinnitus Patient Management. *Ear & Hearing*, 7(6), 390-396.
- Sweetow, R. W., & Henderson-Sabes, J. (2004). The case for LACE: Listening and auditory communication enhancement training. *The Hearing Journal*, 57(3), 32-38.
- Sweetow, R. W., & Sabes, J. H. (2010). An overview of common procedures for the management of tinnitus patients. *The Hearing Journal*, 63(11), 11-15.
- Tonndorf, J. (1981). Stereocilia dysfunction, a cause of sensory hearing loss, recruitment, poor speech discrimination and tinnitus. *Acta Otolaryngol*, 91, 469-479.
- Turner, J. A., Mancl, L., & Aaron, L. A. (2006). Short- and long-term efficacy of brief cognitive-behavioral therapy for patients with chronic temporomandibular disorder pain: A randomized, controlled trial. *Pain*, 121, 181-194.
- Tyler, R. S. (2000). *Tinnitus handbook*. San Diego, CA: Singular Thomson Learning.
- Willott, J. (1996). Physiological plasticity in the auditory system and its possible relevance to hearing aid user, deprivation effects, and acclimatization. *Ear & Hearing*, 17(3), 66S-77S.

Zoger, S., Svedlund, J., & Holgers, K. (2006). The Effects of Sertraline on Severe Tinnitus Suffering - A Randomized, Double-blind, Placebo-Controlled Study. *Journal of Clinical Psychopharmacology*, 26(1), 32-39.